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Docket 091/005

REMARKS

This paper is responsive to the Office Action dated January 16, 2004 which is the second non-final action on the merits of the application.

Claims 1-3, 5-6, 8-11 and 13-23 were previously pending in the application and under examination. Upon entry of this Amendment, claims 5, 10, 11, and 14 are canceled without prejudice, certain claims are amended, and claims 24-36 are added. The added claims fall within the group under examination. Accordingly, claims 1-3, 6, 8-9, 13, and 15-36 are now pending in the application and under examination.

Further consideration and allowance of the application is respectfully requested.

Claim amendments:

Entry of the claim amendments does not introduce new matter into the disclosure. Support for the new claims may be found at various places in the specification, and in the claims as previously presented.

The features appearing in claims 1, 8, and 9 have been incorporated from previous claim 5. Differentiation into highly purified populations of *hepatocytes* and *neurons* is described *inter alia* on page 20, line 18 to page 21, line 13. Promoter sequences that drive expression of protein in undifferentiated hES cells (claims 24-26) are exemplified on page 38 line 40 to page 39 line 1. Particular growth factors and labels that can be expressed in hES cells according to this invention (claims 28-34) are exemplified on page 13, line 35 to page 14, line 2; and page 38 line 40 to page 39 line 1.

Applicant intends to maintain protection for equivalents of the recited hES cells, promoter sequences, and expressed proteins to which they are entitled. Applicant reserves the right to introduce claims to subject matter previously claimed or described in the disclosure in this or any other application.

Double Patenting

Certain claims in the application have been rejected for obviousness-type double patenting over copending application no. 10/039,956. The '956 application no longer contains claims to genetically modified cells. The group elected for examination in the '956 application is a method of

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screening a substance for its effect on cultured cells. Accordingly, there is no double patenting with respect to the claims in the present application with respect to the '956 application.

Applicant acknowledges the provisional non-statutory double patenting rejection over copending application no. 09/530,346. Upon indication that the present application is otherwise in condition for allowance, applicant undertakes to file a terminal disclaimer with respect to the '346 application, or otherwise address this issue.

Rejections under 35 USC § 112 ¶ 1:

Claims 1-3, 5, 6, 8-11 and 17-23 stand rejected under the enablement requirement of § 112 ¶ 1. The Office Action indicates that the specification is enabling for methods of obtaining or producing genetically altered hES cells in the absence of feeder cells on the extracellular matrix. However, the Office Action challenges the scope of the claims because there is no explicit requirement for a fibroblast conditioned medium.

Applicant is grateful for acknowledgement that the specification is enabled to the extent indicated in the Office Action.

Applicant respectfully disagrees that the claims need to be limited in the manner suggested. The Office seeks to limit applicant's coverage to conditions that were exemplified in the working examples. But these are not critical features of the new feeder-free culture method described and enabled by the application.

Federal Circuit case law clearly establishes that a patent applicant is not required to limit coverage to the working examples. Broader coverage is available under § 112 ¶ 1, providing there is no prior art that encroaches on the claimed scope outside the working examples.

For example, *In re Peters*, 221 USPQ 952 (Fed. Cir. 1983) and *In re Rasmussen*, 211 USPQ 323 (Cust. & Pat. App. 1981) both held that applicants are entitled to eliminate a non-critical limitation from the claims in a reexamination application, even though the Patent Office demonstrated in each case that the specification had no working example that omitted the limitation at issue. Similarly, the PTO was found to err when it rejected a claim to an analog of human  $\gamma$ -interferon having only one particular alteration, when the specification taught how to make an analog that had the same alteration in combination with another alteration. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996).

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The specification of the present application clearly indicates that the aspects of the culture system referred to in the current Office Action are not considered critical to the invention. In the section of the Detailed Description dealing with the culture of pPS cells in the absence of feeders, key elements of the medium are indicated on lines 34-37 of page 12:

pPS cells plated in the absence of fresh feeder cells benefit from being cultured in a nutrient medium. The medium will generally contain the usual components to enhance cell survival, including isotonic buffer, essential minerals, and either serum or a serum replacement of some kind.

The description goes on to highlight the use of conditioned medium as a possible nutrient medium to be used in the feeder-free environment. At the time the application was filed, conditioned medium was a preferred embodiment of the invention. For this reason, the manufacture and use of conditioned medium was elaborated, in order to comply with the best mode requirements of § 112 ¶ 1, and in a spirit of full disclosure.

In addition, some of the cell lines used to condition the medium represent an embodiment of the invention for which coverage is being sought in a related application. Such cell lines include any human cell including but not limited to those obtained by differentiating hES cells that have appropriate characteristics to condition medium, which can be identified according to the testing procedure described on page 15, lines 7 ff. Suitable cells may have features that are characteristic of fibroblasts, or other cell types such as mesenchymal cells (page 14, lines 6-10).

However, none of these aspects of the culture environment exemplified in the specification are meant to limit the feeder-free system of the invention (as embodied in the present claims) to the particular culture conditions used in the working examples. By way of this amendment, wording has been incorporated into the specification from priority application USSN 60/213,739. This wording confirms what would already be apparent to the skilled reader — that the feeder-free system can be practiced not only by conditioning the nutrient medium by preculturing with feeder cells, but by synthetically assembling the medium by adding the growth factors directly to fresh medium.

Now that applicant has demonstrated that human ES cells can be established and maintained in a feeder-free environment, working alternatives can be identified and used by the skilled reader. It would be unfair to limit applicant to culture conditions exemplified in the working examples of the present disclosure. By employing the culture test system and the marker assessment protocol provided in the specification (e.g., Examples 1-3), synthetically assembled media can be used and assessed to

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identify effective combinations of culture environment components. The scientists at Geron have confirmed that human ES cells readily grow in fresh (non-conditioned) medium with added growth factors.

Method claims 1 and 17 of the application indicate that the hES cells are cultured in a feeder-free environment comprising an extracellular matrix. Applicant respectfully submits that these claims need not also recite the use of conditioned medium, since this is a preferred embodiment, and not a critical limitation.

Claims 8 and 9 are product claims. The enablement requirement of 35 USC § 112 ¶ 1 is satisfied when the specification discloses at least one method for making the claimed product. Product claims need not be limited to a particular method by which the product was made. By analogy, patents to chemical structures are covered according to the structure, and are not limited to a particular method of synthesis.

Withdrawal of this rejection is respectfully requested.

The Office Action also raises a concern under § 112 ¶ 1, where it indicates that the specification fails to teach that hES cells would give rise to germ line tissue or a whole animal. The meaning of hES as indicated in the specification are lines of pluripotent stem cells derived from a human blastocyst, and having the ability to differentiate into cells of all three germ layers (e.g., page 5, liens 9-22). There is no absolute requirement they be capable of making germline tissue (although it may very well have this capability).

Surely the Patent Office does not mean to suggest that Geron should make a whole (human) animal out of its hES cells, just to demonstrate that the hES cells are totipotent.

#### Rejections under 35 USC § 112 ¶ 2

Applicant gratefully acknowledges withdrawal of the previous rejections made under this Section. Claims 1, 17, 13-15, and 18-19 stand rejected under § 112 ¶ 2 for reasons of clarity.

The claims have now been amended in a manner which is believed to address the issues raised. Claims 1 and 17 do not specify whether the cells were previously grown on feeder cells, only that they are in a culture environment essentially free of feeder cells but comprising an extracellular matrix at the time they are transfected according to the invention.

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Claim 17 also stands objected to for misspelling of the word "the" in part (b). Applicant's copy of the claims previously presented does not appear to contain a misspelling in part (b). Perhaps the confusion has arisen due to a transcription error in the scanning of applicant's previous response.

Withdrawal of these rejections is respectfully requested.

Prior art rejections

Applicant gratefully acknowledges withdrawal of the rejections with respect to publications previously cited from Gearhart et al., and Drey et al.

Claims 8-10 stands rejected under 35 USC § 102(b) as being anticipated by the PCT applications by Pedersen (WO 97/47734).

Claims 1-3, 5-6, 8-10, and 16-17 as previously presented stand newly rejected under § 102(b) as being anticipated by WO 99/20740 (Bodnar et al.). Claims 10, 11, 14, 22, and 23 as previously presented stand newly rejected under § 103(a) as being obvious over WO 99/20740 in combination with an article by Feng et al. (J. Molec. Biol. 292:779, 1999).

Claims 8 and 9 as previously presented stand rejected under § 103(a) as being obvious over a combination of Thomson (Science 282:1145, 1998), and Bradley et al. (U.S. Patent 5,614,396).

Applicant respectfully disagrees that the Pedersen reference affects the patentability of the claimed invention, for reasons indicated in the previous response. The reference does not enable the making of genetically modified hES cells, which is required to maintain a rejection under §§ 102 or 103. "In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 USPQ2d 1301 (Fed. Cir. 1989). The Pedersen reference contains no working example, and any suggestion to make genetically modified human ES cells must be inferred from work with genetically modified mouse ES cells.

However, the Thomson article (along with U.S. Patent 5,843,780 by Thompson) indicate that primate ES cells are much more dependent on embryonic feeder cells to prevent differentiation than mouse ES cells, which will grow in an undifferentiated form in a medium containing LIF. Neither the Pedersen reference, the Bradley patent, nor the Feng reference offer a practical solution of how to produce a population of genetically altered human ES cells, while having to maintain the cells on feeders according to the teaching of Thomson.

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Furthermore, the claims pending in this application as amended are distinguished over the all of the cited art for several reasons, including the following:

Claims 1, 8, and 9, and their dependents now require that the genetically altered hES cells have the property of expressing a protein encoded in the transfected polynucleotide while in the undifferentiated form. This is made possible because the encoding region for the expressed protein is operably linked to a promoter that promotes transcription of the encoding region in an undifferentiated hES cell. Since hES cells undergo considerable change in the profile of genes expressed when they undergo differentiation (US 2003/0224411 A1), a promoter that drives expression of a gene in a differentiated cell will not necessarily also drive expression while the hES cell is in the undifferentiated state.

Identification of promoters that drive differentiation while the cells are in the undifferentiated form is a useful finding. It allows genetically altered cells to be generated, selected, and enriched while the cells have the virtually limitless replicative capacity of the undifferentiated phenotype. This in turn makes it possible to obtain populations that comprise 25% or 90% genetically altered cells before differentiation. The present disclosure exemplifies promoters that cause protein expression in undifferentiated hES cells, and explains how promoters with this property can be identified and selected (e.g., Examples 5 and 6, pages 25-28).

Claim 17 and its dependents now require that the genetically altered hES cells be differentiated into hepatocytes or neurons. None of the cited references teach how to differentiate hES cells into populations that are predominantly either of these particular cell types.

Withdrawal of all rejections under 35 USC §§ 102 and 103 is respectfully requested.

Request for Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

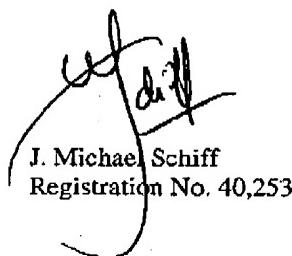
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Fees Due

Accompanying this Amendment is a fee calculation sheet, authorizing the Commissioner to charge the Deposit Account for the added claims not previously paid for.

Should the Patent Office determine that an extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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